Author's response to reviews

Title: Temporal Aggregation Impacts on Epidemiological Simulations Employing Microcontact Data

Authors:

Mohammad Hashemian (mohammad.hashemian@usask.ca)
Weicheng Qian (weicheng.qian@usask.ca)
Kevin G Stanley (kevin.stanley@usask.ca)
Nathaniel D Osgood (nathaniel.osgood@usask.ca)

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Author's response to reviews: see over
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Dear Adrian Aldcroft,
Executive Editor
BMC Medical Informatics and Decision Making

Please find our revised manuscript “Temporal Aggregation Impacts on Epidemiological Simulations Employing Microcontact Data,” by Mohammad Hashemian, Weicheng Qian, Kevin G. Stanley and Nathaniel D. Osgood (MS: 1839910165754579). We would like to thank the reviewers for their insightful reviews. We have done our utmost to address their concerns within the scope of the contribution of this paper.

We felt in general that both reviewers liked the paper. We have made several textual changes and added depth and clarification where requested. We have also added a section from one of our earlier papers (http://www.biomedcentral.com/1472-6947/12/35) to address reviewers' questions about the structure of our data set. While we are reluctant to reproduce previously published work, we have done so here to increase the readability at the request of the reviewers.

Attached to this letter are the specific responses to each reviewer. Please do not hesitate to contact myself or any of my co-authors if you have questions pertaining to the paper.

Sincerely,

Kevin Stanley
Assistant Professor
Response to reviewer Armin Mikler

- The reviewer commented, “For example, I would have liked to see why the estimated number of realizations of 10,000 was deemed sufficient (or maybe an overkill).”

This is a valid comment. The following text was added.

*Based on the 100,000 run ensembles with the same model and dynamic network reported in [24] we concluded that 10,000 runs were sufficient, as the maximum depth of infection in [24] was reached 10 times, implying that division by 10 would have a high probability of capturing even the most extreme infection events, while maintaining the probability distribution at significantly reduced computational cost. Because each run could be conducted relatively swiftly (typical run-times for an ensemble were 30 s) having a large number of runs was not computationally prohibitive given the resources available to us.*

- The reviewer commented, “While the authors could use a graph structure to highlight how the sampling of contacts will be translated into a graph form. Not all readers can be expected to be familiar with graph theoretical concepts.”

The reviewer raises a valid point that pertains to publishing in a multi-disciplinary venue. We have added the following text in an attempt to clarify the role of the graph representation.

*The dynamic contact network can be visualized as a series network where the nodes represent participants and each connections represents a pair of participants that were proximate to each other during a time step. This construct is often called a dynamic graph – drawing from the field of Graph Theory – where the participants are nodes, and the connections are the edges. This dynamic graph can be realized in practice as a three-dimensional matrix.*

- The reviewer commented, “More importantly figures deserve to be introduced in more detail, particular the reference to figure-2 as it contains 4 different graphs. I suggest a separate discussion of figure 2a, 2b,….

The following text was added to figure 2’s caption.

*This figure provides a heat map to demonstrating the distribution of generated aggregated contact durations used in the simulation. Each sub-graph represents the CCDF of contact duration for: a) the empirical distribution used in the FullA case; b) the two part power-law exponential distribution commonly used in practice; c) the three part power law-exponential-exponential distribution which provides a better fit to our data; and d) the best fit power law-exponential-exponential with outliers included as single empirical data points. The shade of the point represents the frequency with which a network contained exactly that contact duration-probability pair. Some slight fanning of the distribution in b, c and d at higher contact durations indicates that our network construction algorithm had good but not perfect reconstruction of contact durations when compared to the empirical baseline.*
Additionally, a more detailed exposition of the structure of the Flunet dataset has been added to the start of the results.

- The reviewer commented, “The caption of figure 3 does not make any sense and must be corrected. Further, the construction of figure 3 as a multi-segment fit should be explained in more detail.

The caption for figure 3 has been changed to

**Figure 3 - Curve fitting methods of Aggregated Contact Duration**

This figure shows the four piece-wise fitting approaches for aggregated contact duration over a CCDF plot of the empirical data. Points represented by a (+) are indicative of the empirical probability of a contact duration. The solid red line corresponds to the two-piece power law-exponential distribution fit. The solid green line corresponds to the three-piece power law-exponential-exponential fit. Text in blue or red corresponds to the break points for each fit. Outliers not included in either fit are included in the SW3PTT case.

The following text was added to the paper:

*Fitting of distributions was performed using linear regression in MATLAB. For linear regression to perform properly, data underwent log-log (power law fitting) or log-linear (exponential fitting) transformation prior to performing the piecewise fit. For fitted distributions, the fitted curves were required to achieve a \( R^2 \) value exceeding 99%. Piecewise breakpoints were selected by iteratively changing the breakpoints, performing the regression, and manually selecting the point at which error began to increase sharply, but which still maintained a minimum \( R^2 \) of 99% value for all the piecewise components.*

- The reviewer commented, “All figures should have a caption that summarizes their purposes. All figures have had their captions expanded to be more in keeping with standards for the medical literature.”

We initially opted for the terser figure captioning and descriptions common in the applied sciences. Figure captions have been updated to be more in keeping with the style of the journal.

- The reviewer commented, “Some of the terms should be defined in more detailed and not left to the interpretation of the reader. For example, it is not clear what identifies “low-risk individuals”

The sentence was amended to the following.

*Although reasonable matches exist for low-risk individuals (characterized by fewer infection counts in both the FullD and selected DayD cases), typical day techniques overestimated the infection risk for higher-risk individuals, leading to weaker correlations*
The reviewer noted a number of wording and grammatical corrections. These have been addressed as the reviewer suggested.

- The reviewer commented, “On page 8, the phrase “The study ran from ....” reads oddly!”

The sentence has been changed to

*The study was conducted between November 9th, 2009 and February 9th, 2010 – a time period coinciding with the second rise of reported H1N1 cases in the province of Saskatchewan [30].*

- The reviewer commented “On page 18, the sentence “....by different distributions than....” should probably read “....rather than...”

This has been changed as suggested.

- The reviewer commented “After a thorough discussion, I feel that what is titled conclusion should be renamed as Summary as it really does not offer as much a conclusion as a recap of the findings.”

This has been changed as suggested.
Response To Reviewer Wen Dong

- The reviewer commented, "What does the proximity network of the 36 subjects look like and how does the network change over time? It won’t hurt to give some details about the data as in the paper "FLUNET: Automated Tracking of Contacts During Flu Season", as well as how the network evolve."

Both reviewers requested additional details about the structure of the dataset. While we wished to avoid replicating published work, given the reasonable requests for the sake of readability we have added an additional paragraphs to the beginning of results describing the properties of the data set in more detail. These paragraphs and associated figure were reproduced from [24].

- The reviewer commented “Was the proximity network similar in the major holiday (Christmas & new year) and (perhaps) the end of a semester during the experiment as compared to ordinary school days? If the network is dynamic over time, then the over-estimation in the aggregated networks reported in the paper is perhaps due to a flaw in experiment design, rather than the methodology itself.”

The reviewer is correct to note that the contact patterns over the holiday season (Christmas and New Years) were substantially different than the contact patterns during either semester. We would argue however that the reviewer is incorrect in asserting that this implies that our results are an artifact. Substantial breaks in contact patterns occur either stochastically due to individual’s life circumstances (getting a promotion, going on parental leave, taking a vacation) or more regularly due to physical or cultural norms (societal holidays, work-break cycles). The fact that typical aggregate representations do not capture these dynamics is one of the findings we highlight in our paper. While we are the first to note this behavior in empirical data, similar findings have been reported when comparing agent-based and population level models in purely synthetic systems. The primary issue is the temporal clustering of contacts within the dataset that is captured in the dynamic network, but ignored in the aggregate network. This raises the natural question of what sampling rate is appropriate for a given pathogen. We have not addressed this question specifically in the paper, but dimensionality considerations offer some insight. For very short-lived pathogens, a typical day approach may be sufficient in that all members of the network will be infected quickly or the transmission will peter out. For long-lived pathogens such as tuberculosis, an aggregate model may be appropriate, as infection rates are low and latent periods are very long. For the flu-like infection we modeled, it would seem that typical days are too short and aggregate representations are too long.

To better address the issue of contact patterns over the holiday period, the following text was added to the section describing the data set at the beginning of the results section.

*While the contact densities in 2.a hold in general for those times when contact occurred, normally weekdays, they do not adequately capture the patterns on the weekend or during holidays (particularly the week between Christmas and New Year’s Day) which are characterized by more sporadic or sparse connections. However, it is worth noting that these gaps in connectivity relate to the underlying contact patterns of the sample, which are*
characterized by primarily professional relationships. While we cannot claim that a given participant will have a diminished chance of infection over a weekend or holiday, we can claim with a great deal of certainty that they will have a diminished chance of becoming infected by a co-worker during those time periods.

To better address the interaction of disease and contact dynamics, the following text was added to the discussion.

*For very short-lived pathogens, a typical day approach may be sufficient in that all members of the network will be infected quickly or the infectious transmission will dwindle quickly. For long-lived pathogens such as tuberculosis, an aggregate model may be appropriate, as infection rates are low and latent periods are long. For the flu-like infection we modeled, our results indicate that typical days are too volatile and aggregate representations too permissive.*

- The reviewer commented, “Did the 36 subjects interact with those in different research groups, or they just form 7 clusters corresponding to the 7 research groups?”

While there was obviously a large degree of clustering within laboratories and offices, bridging individuals did exist which spent significant time with 2 or more research groups. Additionally, most students had brief, less frequent contact with other students and staff when for example stopping in the main office to get physical mail, attending a class, or eating lunch in the graduate lunchroom or one of the cafeterias.

This has been addressed in the new section of the results, in particular Fig. 2c and its accompanying text.

- The reviewer commented “The authors can help the readers to get more truths of "aggregating dynamic network" by doing the following, supposing the proximity records are (person A, person B, time stamp in 30 seconds increment)...”

We had some difficulty parsing the precise methodology the reviewer wished us to employ in the recommended analysis. I have paraphrased the comment below to demonstrate our understanding of the request. If this understanding is incorrect, we would be happy to open a dialog with the reviewer address his concerns.

- The reviewer wishes to know the impact of maintaining the day, or week ordering, but shuffling the contact patterns within that day or week to investigate the impact of temporal clustering and ordering on disease transmission.

This is a reasonable request, as it would speak directly to the impact of ordering. However, if the random shuffling draws from a uniform distribution, then it is mathematically equivalent to the day (DayA) and full (FullA) aggregate cases discussed in the paper. The additional knowledge that could be gained would be the impact of the scale of the temporal aggregation, which is not the purpose of the submitted paper. As noted above, we suspect the impact of the scale of aggregation is strongly dependent on the disease being modeled. Disease-scale interactions, and by extension disease-sampling rate interactions are not the
subject of this paper. We are in fact currently investigating this very complex interaction with multiple data sets over multiple pathogens as the subject of another paper, which should be submitted this year. As addressing this request directly would create more questions than answers in the paper, we have not performed the additional simulations requested, and instead described the more fulsome solution we are working on in future work.

To better address the mathematical generalizability of our analysis the following text was added to the end of the Methods section.

*Infectious events were generated with according to a Poisson process as described in [24]. In the FullD and DayD cases, the state of the contact graph at the time of an agent generating an infectious event was queried, and connected agents were infected based on the probability of infection for the pathogen. For aggregate representations a joint probability of the edge weight from the static graph and infection probability was used to determine infection probability. This is mathematically equivalent to randomly sampling the contact records from either the DayD or FullD contact records for the DayA and FullA cases.*

To better address the scope of the claims of the paper the following text was added to the summary.

*However these findings are limited by the number of participants in the study and the single pathogen studied.*

*We will also investigate the interaction between pathogen behavior and temporal sampling strategies.*

The reviewer commented “The mathematical details of the simulation on the Social Evolution data set, which is similar to FluNET data, can be found in the following paper:”

This paper has been added. We would also like to encourage the reviewer to examine the reference list in this paper, as many references relevant to his future work are present, which were not captured in his recent paper. Currently, the field is highly fragmented and there seems to be multiple paper genealogies in circulation that should be merged as the discipline moves forward.